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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
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United States of America

Hamburg, April 3, 2000

Comment on Draft Guidance for Photosafety Testing

Docket No. 99D-5435, CDER 9967

Dear Sirs:

We are often confronted with the problem of selecting a design for testing of photoallergenic potential in humans which is acceptable for registration purposes. On the basis of the literature it can be concluded that a maximized design is most sensitive for delivering information about allergenic potential. To our knowledge, maximized test designs employing 2-3 minimal erythema doses are still accepted for registration purposes. For scientific as well as ethical reasons we do not consider such methods satisfactory. We have developed an alternative method for a maximization test for testing photoallergenic potential of topically applied drugs which we would like to present for consideration.

With best regards,

Hughes-Formella

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Enclosures

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Alternative Maximization Test for Testing of Photoallergenic Potential of Topically Applied Products

In the draft guidance for photosafety testing (posted January 7, 2000) it is encouraged to submit specific data that may help in evaluating the regulatory acceptance of human studies for evaluation of photosensitivity. We would like to bring to your attention an alternative to the widely used "photomaximization test" for identification of photoallergic contact sensitizers designed by Kaidbey and Kligman [6]. This model is still used for testing photoallergic potential for registration purposes. The proposed alternative design is based on recent knowledge about immunosuppressive effects of UV radiation, results obtained from animal models for testing photoallergenic potential and the principles set down by Kligman advocating maximization testing for allergenic potential.

The pathogenesis of contact photoallergy and contact allergy is similar except that ultraviolet (UV) radiation is necessary for the induction and elicitation phase of a photoallergic response [1]. Radiant energy is required to produce a photoantigen which then induces the immune response [2]. Therefore the principles laid down by Kligman [3-5] for detecting contact allergens largely apply for detection of photoallergens.

Kaidbey and Kligman published a photomaximization procedure for detection of photoallergens in 1980 [6]. The method is a modification of the maximization test for contact sensitizers described by Kligman and Epstein in 1975 [7]. In the photomaximization procedure [6] the test substance was applied for 24 hours followed by exposure to 3 Minimal Erythema Doses (MED) of solar simulated radiation twice weekly for 3 weeks in a panel of 25 Caucasians. The subjects were challenged 10 - 14 days after the last exposure by application for 24 hours to a fresh area of normal skin followed by exposure to 4.0 J/cm^2 UVA. The test sites were assessed 48 and 72 hours later.

Exaggerated drug exposure is achieved in both the maximization test for contact sensitizers and the photomaximization test by induction of inflammation at the test site. Chemical or physical inflammation, if not too severe, enhances contact sensitization [3]. The inflammatory reaction may serve to enhance the response to contact sensitizers by increasing the skin permeability [4,8,9], causing the release of inflammatory mediators at the test site [10] or promoting the recruitment of immunologically competent cells to the test site [8]. Kligman [4] assessed the effectiveness of various insults and concluded that 24 hour occlusive pretreatment with sodium lauryl sulfate (SLS) was superior to other methods, including irradiation with 2 MED. In fact, it was demonstrated that sharp UV erythema, without blisters or exudation, is scarcely better than application to normal skin [4]. In the photomaximization test described above SLS was not used since repeated exposures to 3 MED resulted in intense inflammatory reactions by the second exposure [6].

In the alternative test procedure described here an optimized photomaximization test design is presented which takes into account the principles for a maximization test as set down by Kligman [4,5] while allowing for more recent developments in irradiation biology. The major modification of the photomaximization design by Kaidbey and Kligman [6] is the use of SLS to induce irritation in the test sites rather than induction of inflammation by repeated doses of erythemagenic radiation.

On the basis of current knowledge on the suppressive effects of UV irradiation on the skin's immune response [11-19], there is a need for a modification in the Kaidbey and Kligman test design [6]. Low doses of UVB radiation in humans lead to a reduction in effective sensitization [11,12] as well as an enhancement of tolerance to topically applied antigens [12]. The suppressive effect of UVB on the induction phase of contact hypersensitivity is evidenced when a chemical hapten is applied on irradiated skin. The effect is probably initiated by a direct effect of UVB on Langerhans cells, the major antigen-presenting cells in

the skin, which results in reduced antigen-presenting capacity [19]. In addition to effects on Langerhans cells, a population of UV-induced macrophages appears in UV-exposed epidermis in humans [20] which are responsible for the preferential activation of suppressor cells [21].

Evidence for the impairment of Langerhans cell function following *in vivo* irradiation of human skin with 3 MED UVB was recently reported by Dittmar et al [18]. Cooper et al. [12] convincingly demonstrated that UV exposure in humans results in highly significant, dose-responsive decreases in immunologic responsiveness which leads to diminished ability to mount a form of delayed-type hypersensitivity (contact sensitivity) if the initial immunization occurs in UV-exposed skin. These authors assessed dinitrochlorbenzene (DNCB) contact sensitivity in human skin following administration of four repeated doses of suberythemagenic (0.75 MED) and erythemagenic (2 MED) UVB. There was a reduction in the frequency of strongly positive responses from 73 % in the control group to 5 % in the group receiving 2 MED and to 32 % in the group receiving 0.75 MED. Significant reductions in Langerhans cells and an increase in $CD1a^{-}DR^{+}$ macrophages were measured in punch biopsies from the subjects receiving the erythemagenic doses [12].

The need for radiation in the UVA (320-400 nm) range for the induction and elicitation of a photoallergic reaction is well established. The UVA dosages proposed in the accompanying protocol are within the accepted margins [22]. In contrast, the need for UVB radiation at all is controversial [discussion in 1]. It has been speculated that the nonspecific skin damage induced by UVB is responsible for the enhancement of photoallergy in some experimental models [1]. For example, in one study UVA and UVB radiation during the induction phase were necessary for the induction of a photoallergy to tetrachlorosalicylanilide (TCSA) in guinea pigs [23]. In other studies a photoallergic response to TCSA could be induced in guinea pigs with UVA only when the induction sites were pretreated with Freunds' adjuvant [24] or the irritant SLS [9]. In order to optimize this test design we have included one test field which will be irradiated with 10 J/cm² UVA alone and one field which will be irradiated with 10 J/cm² UVA
and approximately 0.75 MED UVB. This is in keeping with the suggestion for screening of photoallergenic potential made by Gerberick and Ryan [1]. These authors concluded that when using the mouse ear swelling photoallergic protocol, UVB and UVA radiation should be included for both the induction and challenge phases to obtain an optimal photoallergic response. These authors intentionally employed low UVB doses in this model, minimizing the risk of immunosuppressive effects.

We have performed the modified test design for photomaximization using 2 % SLS and suberythemagenic UV doses on several occasions. Scoring of the degree of irritancy during the induction phase ensures that sufficient irritant reactions are present for a maximization procedure. Further, no intense inflammatory reactions occur such as the reactions necessarily induced in the original photomaximization procedure [6]. Kaidbey and Kligman described the reactions occuring during the induction phase as follows:

> "Intense inflammatory reactions developed by the second exposure as would be expected from repeated three MEDs of sunburning radiation. An intense erythema was present after the first week. In very fair individuals, blistering occasionally developed after the second or third exposure, following which the epidermis peeled off. Erythema, edema and crusting were present by the end of the second week. Scaling and pigmentation developed during the third week."

In light of the discomfort which must accompany such reactions, even if limited to small treatment sites, as well as possible undefined adverse effects which may accompany repeated irradiation with clearly immunosuppressive doses of UVB, the photomaximization procedure proposed in the accompanying protocol is clearly superior to designs utilizing higher MEDs.

In conclusion, the optimization of designs for testing of sensitization and photosensitization potential in humans can only be achieved on the basis of literature review and ethical issues. On the basis of current knowledge as well as for ethical reasons, the use of repeated doses of 2-3 MED UVB radiation should be avoided when testing photosensitizing potential. The method presented here provides an alternative to the Kaidbey and Kligman model [6] which is scientifically sound. A publication outlining the advantages of the model presented here is in preparation.

Experimental Procedure

Subjects

Twenty-four healthy adult male or female volunteers ranging in age from 18 to 50 years participate per panel. All subjects should be Caucasian with skin types I, II or III. Exclusion criteria include moderate to severe acne, suntan, eczema, hyperpigmentation or tattoos in the test fields; history of hypersensitivity to the study medication or to drugs with similar chemical structures or to other components of the study medication; history of hypersensitivity to the adhesive tape used to fix the test chambers; treatment with systemic or locally acting medications which might counter or influence the study aim within two weeks before the beginning of the study or during the study (e.g. antihistamines, glucocorticosteroids, potentially photosensitizing drugs such as thiazides, non-steroidal anti-inflammatories, sulfonamides, tetracycline, etc.); multiple pigment nevi; or a known hypersensitivity to light (UVA, UVB) or a photodermatosis.

Light source and exposures

The radiation source for UVA light is a metal halide sun simulator UVASPOT 1000 with H1 filter for pure UVA light (manufactured by Dr. Hoenle, Martinsried, Germany). A surface dose of 10 J/cm² which is beneath the minimal erythema dose for UVA is used during the induction phase. During the challenge phase 5 J/cm² UVA is used. Exposure intensity is 40 mW/cm² UVA. To set this intensity the distance of the source from the plain of the surface which is to be irradiated is adjusted before every irradiation series using a UVA/B meter (UVA/B meter, manufactured by Dr. Hoenle, Martinsried, Germany).

The radiation source for UVB light is a UV 800 lamp (Waldmann, Villingen-Schwenningen, Germany). The MED for a fair-skinned individual is used to calculate the time required to achieve 0.75 MED. The same irradiation time is used in all individuals since small variations in irradiation intensity are not relevant for induction of photosensitization reactions. Even surface lighting with an intensity of 2 mW/cm² UVB is used. To set the required intensity the distance of the source from the plane of the surface to be irradiated is adjusted before every irradiation series with a UVA/B meter (UVA/B meter, manufactured by Dr. Hoenle, Martinsried, Germany).

Induction

During the induction phase three test sites on the back are treated with each test product. Before each application of the test products the test fields are treated with sodium lauryl sulfate 2 % (SLS). The SLS is pipetted into Finn® Chambers (18 mm inside in diameter) containing a filter paper and then applied to the back. The test chambers are fixed in place using adhesive tape. Twenty-four hours later the chambers are removed and approximately 200 µl of each test product is applied to the three sites in fresh Finn® Chambers. Tuberculin syringes are used for dosing. The occlusive coverings are removed from two of the sites 24 hours later and the sites are cleansed by gently wiping with a soft disposable tissue. These two sites are then irradiated with 10 J/cm² UVA. Subsequently one of these sites is additionally exposed to approximately 0.75 minimal erythema dose (MED). Following the irradiation the occlusive covering is removed from the third site and this site is cleansed. This sequence is repeated twice weekly over three weeks for a total of six treatments and six UV exposures. Treatments are always applied to the same test sites. The first treatment cycle begins on a Monday with application of SLS. On Tuesday the test products are applied. Following irradiation on Wednesday the second treatment cycle is begun without a rest period. Following irradiation on Friday the irradiated sites are left open until the following Monday. The nonirradiated field is covered with a nonocclusive light impermeable bandage during this rest period.

Challenge

The subjects are challenged 10-17 days after the last exposure. During the challenge phase SLS 5 % is applied occlusively for one hour to three fresh test sites on the back. The chambers are then removed and approximately 200 μl of each test product is applied to the three sites in fresh Finn® Chambers. Twenty-four hours later the occlusive coverings are removed from all three sites and the areas are gently wiped clean with a soft disposable tissue. One of the sites is immediately covered with a nonocclusive light impermeable bandage which remains in place between clinical assessments for the duration of the test period. The other two sites are then irradiated with 5 J/cm^2 UVA. Subsequently one of these sites is additionally exposed to approximately 0.75 MED.

Clinical assessment

During the challenge phase dermal reactions are scored immediately, 24, 48 and 72 hours following irradiation according to the following five-point scale:

0 = no reaction
1 = erythema
2 = erythema with infiltration
3 = erythema with papulovesicles
4 = erythema with blisters, blebs, erosions

The same scale is used to assess the treatment fields following each of the six treatment cycles during the induction phase. During this phase it is expected that an irritant reaction with reddening will be induced by application of SLS. The assessment scores recorded during the induction phase only serve to document the presence of the desired irritant reactions and are not relevant to the assessment of allergenic potential.

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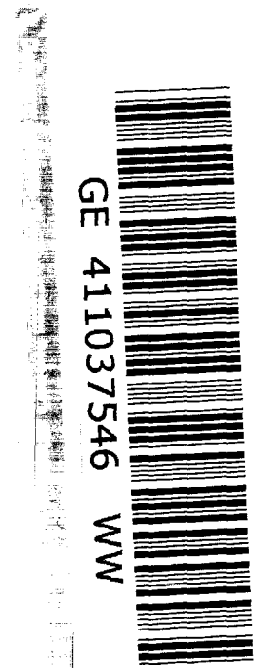

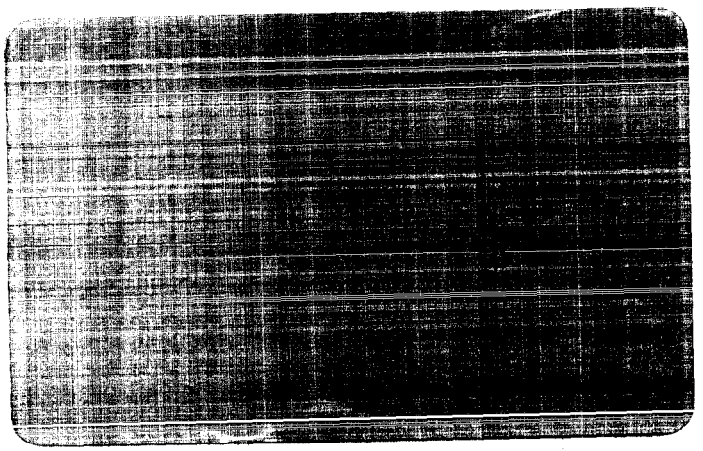

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